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Médicament

Supercritical Fluids Division

FORMULCOAT®: A SOFT AND "SOLVENT-FREE" COATING PROCESS FOR TASTE MASKING OF BITTER DRUGS

In this paper, Hubert Lochard, PhD, R&D Supercritical Fluids Projects Manager, Pierre Fabre Medicament, describes the company's proprietary supercritical fluid coating process, Formulcoat®, and its application in taste-masking in particular orodispersible tablet formulation. Results from coating ibuprofen using the Formulcoat® process are presented.

A significant number of active pharmaceutical ingredients (APIs) are bitter tasting. This bitterness is not an issue in the forms such as capsules and tablets which are swallowed whole. However, many patients are unable to swallow tablets. These include: people suffering from dysphagia with mechanical, neurological or muscular causes; people who are prostrate; and many elderly and paediatric patients.

For these people, where only solid oral dosage forms are available, crushing the tablet is often the only way for them to take their medicine but this is not advisable for various reasons, including safety, and the problem of the unpleasant bitter taste is not easily solved. Studies performed in hospitals have shown that even if these patients crush the drug and add juices, or put the crushed dosage form into food such as fruit compote, this is not enough to mask the bitter taste.

It is therefore necessary to develop alternative oral formulations such as liquids, effervescents and oro-dispersibles.

Formulation of active ingredients in alternative oral forms like these is a challenge, especially for improving patient compliance. Among the various alternative oral forms, rapid-disintegrating / orodispersible delivery systems seem to be attractive for patients. Nevertheless, because of the bad taste of a lot of pharmaceutical molecules, this type of formulation is an issue. Coating appears as a solution for treating these ingredients.

Taste masking chemical systems (sweeteners, flavours) are highly developed, but some of these formulation methods do not work very well (astringency due to the high amount of acid) or complicate the process for preparing tablets. Some require high levels of polyols, which have a laxative effect rendering them unsuitable for repeated administration over long-term treatment.

Sometimes, the quantity of sweeteners and flavourings needed to achieve correct taste masking is such that it does not allow the dosage form development in an orodispersible form because the volume of disintegrating tablet in the mouth is then very large and may contain only 30% or less of active ingredients. Furthermore, the use of sweeteners and flavours complicates and increases the cost of the formulation.

Using organic solvents, these techniques do not always give excellent results in terms of taste masking, and do not fully meet the challenges of formulators (in terms of results and cost optimisation). Conventionally, coating has generally been carried out using techniques such as electrolysis, vapour deposition, and fluidisation. Yet all these methods have limitations including inability to coat small particles due to electrostatic charge build-up, risk of forming explosive vapour phase mixtures when organic solvents are used with air as the fluidising medium, and adverse environmental effects of volatile organic compound (VOC) emissions that require destruction by expensive downstream incineration units.

Clearly, there is a need for environmentally benign and inherently safe coating pro-

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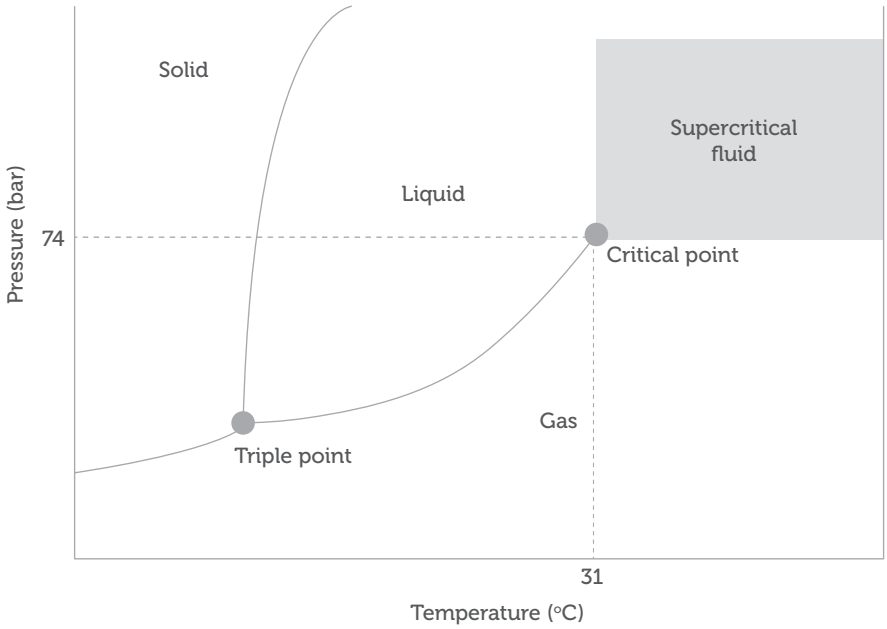

Figure 1: Carbon dioxide phase diagram.

cesses. Within the past two decades, supercritical carbon dioxide has been investigated as a benign medium for coating substrates.

The Formulcoat® process consists of a physical masking of each particle and therefore gives excellent taste masking and allows the formulator to work on the usual base of formulation. Formulcoat® does not delay the solubilisation of the API and permits a formulation high in active ingredient, requiring only 5% excipient for some APIs.

The present work reports the design, construction and demonstration of a cGMP pilot-scale CO_2-based coating equipment for pharmaceutical applications. It will present two examples: the first is the coating of pseudoephedrin, a decongestant that shrinks blood vessels in the nasal passages; the second is a taste-masking application on ibuprofen, a non-steroidal anti-inflammatory drug that presents a bitter taste.

Formulcoat®, a novel proprietary, patented supercritical CO_2 process, has several advantages as follows:

- operation at ambient temperatures wherein degradation of the active pharmaceutical ingredient is avoided
- the ability for defining layer thickness of excipient
- coating process without use of organic solvents.

A fluid is in a supercritical area when both temperature and pressure are above its critical values. Supercritical fluids present a density similar to the liquids and are gas-like concerning viscosity. Therefore material and heat transfers are fast and efficient. Properties of these kinds of fluids are easily modified by slightly tuning pressure and/or temperature.

Carbon dioxide is often used because it is a solvent non-toxic, cheap, easily available and its critical point is easy to reach (31°C, 74 bar). Supercritical carbon dioxide is considered a "green" solvent: another important feature is that at room conditions, carbon dioxide is a gas, that means that after process, a simple depressurisation allows to

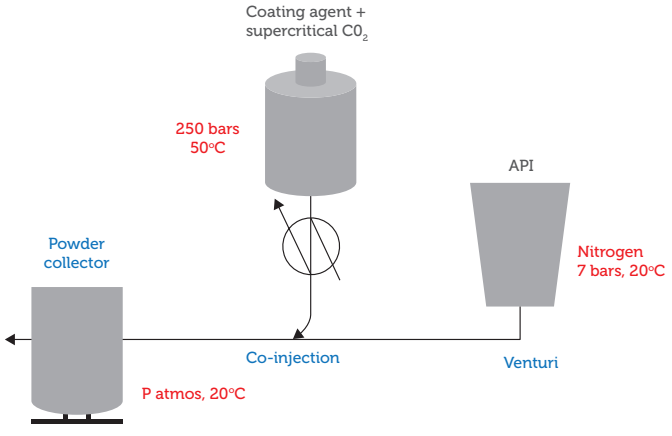

Figure 2: Schematic view of Formulcoat® process.

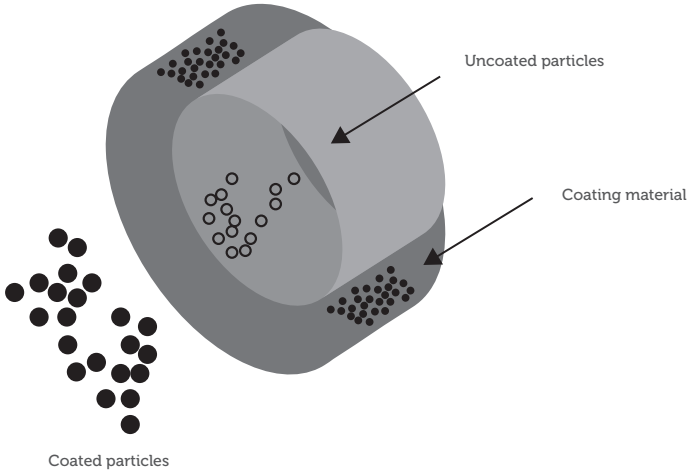

Figure 3: The co-injection device, which ensures contact between the native particles and the coating material expanded from the high-pressure vessel.

obtain powder without any residual solvent (Figure 1, previous page).

Supercritical fluids and especially supercritical CO_2 display excellent solute properties for a large range of materials and were found to be helpful to generate solvent-free particles. Briefly, the process involves the dissolution of a 150 bar dense gas into a liquid or a molten fatty solid until its saturation (Figure 2, previous page). The expansion of such a saturated solution or molten phase creates a high super saturation and a sharp temperature decrease leading to particle or droplet formation. API particles then come into contact with the expanded coating agent via designed co-injection device, as shown in Figure 3 (previous page). Due to the high supersaturation generated, fatty agent solidifies onto the particles. The coated particles are then conveyed to a gas/solid separation filter. After expansion, CO_2 becomes gaseous and is easily separated from the processed material.

One specific advantage of Formulcoat® is that the API particles are kept at ambient temperature and therefore are prevented from any degradation. The contact between the native particles and the pulverised fat occurs in a "in house-designed" co-injection device, which further allows the deposition of the coating onto the particles. The native particles are conveyed to the co-injection device by a Venturi system fed by pressurised nitrogen.

Full capacity of the c-GMP pilot-scale unit is 10 kg of coated powder per hour.

Formulcoat® leads to a thin-film deposited onto the particles. The homogeneity and the thickness of the coating layer depend of course of process conditions and on the nature of the excipient, particularly its filmogenicity. The usual coating agent is Precirol®: a GRAS commercial agent used for taste masking.

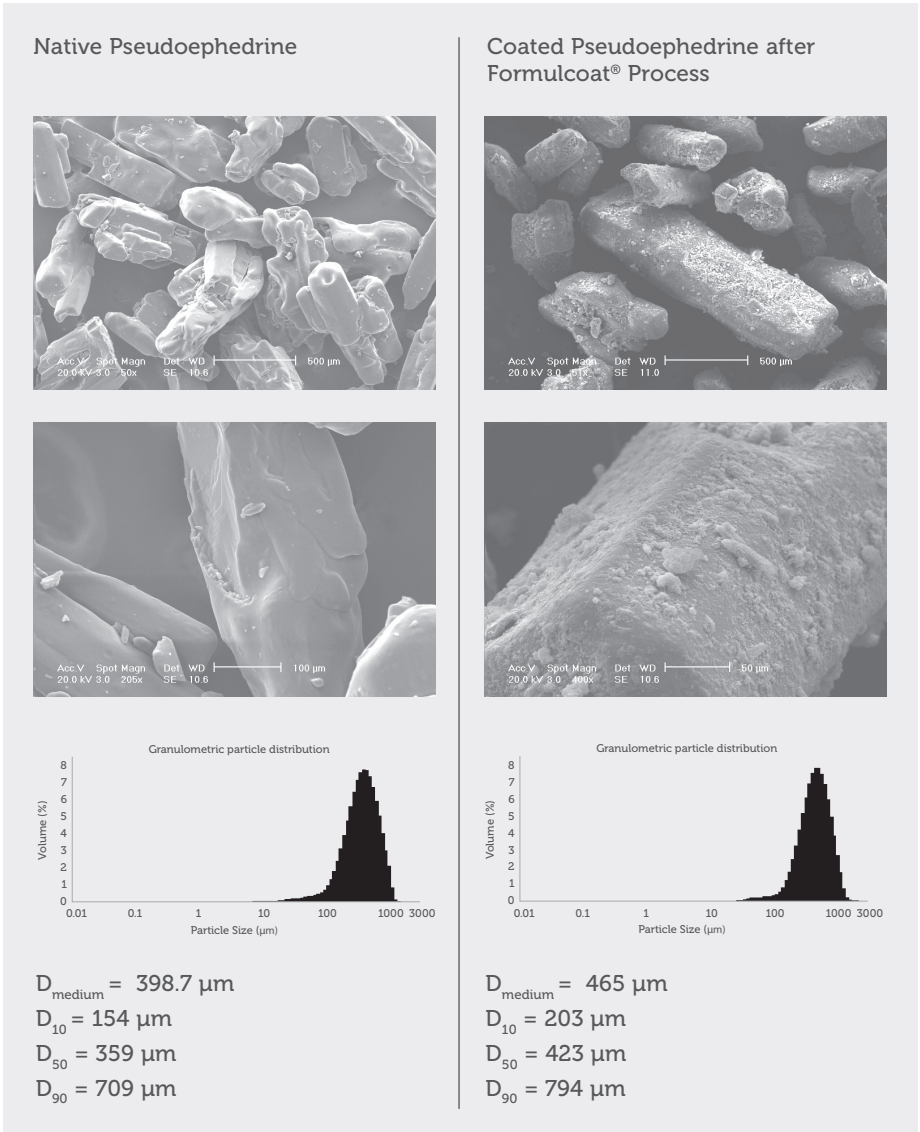

Figure 4: Granulometric properties and SEM images of pseudoephedrine before (left) and after (right) Formulcoat® processing using 9% of Precirol®.

Figure 4 presents granulometric properties and SEM pictures of pseudoephedrine before (left) and after (right) Formulcoat® using 9% of Precirol®.

We can see that a thin film deposited onto the particles leads to an increase of their average diameters, the minimal thickness of the layer is 3 µm. Particle-size distribution showed a narrow polydispersity for this compound, which was confirmed by microscopy. The process does not alter the particles, neither by attrition nor by agglomeration. For applications in taste masking, a small amount of coated agent is usually chosen (until 10%), in order to maintain immediate release (i.e. avoid sustained release).

Tests were also performed successfully on granulated ibuprofen from Pharmatrans Sanaq AG (Allschwil, Switzerland). Efficient taste masking, checked in a taste-panel session, was obtained with 4% Precirol®. Drug release tests were performed and samples present similar dissolution rates compared with raw materials. Ibuprofen content was verified by HPLC and the homogeneity of the coating was verified by IR-Raman Spectroscopy (Atomic Force Microscope Alpha 300 AR, WITec, Ulm, Germany) and SEM imaging. The coating process is homogeneous and leads to a 6 µm Precirol® film deposited onto the particles (Figure 5).

Powder physical characteristics and ibuprofen dissolution profiles were determined:

- Particle size distribution (D50 = 253 µm)
- Bulk density = 0.459
- Tapped density = 0.515.

The USP dissolution profile (pH 7.2) shows a limited slow release effect and met USP dissolution requirement (NLT 80% % ibuprofen release until 60 min). Finally, the coated Formulcoat® ibuprofen has low bitterness and good formulation properties. No agglomeration phenomena occur.

CONCLUSION

To conclude, the supercritical technology presented in this article is a green process for coating formulations, which shows many advantages. This process is mild, without any use of organic solvent, and cost-effective. Furthermore, results obtained by this technology in terms of opportunities to coat small particles efficiently, are often better than those obtained by conventional processes.

The process allows producing kilogram batch scale of coated particles. It could be

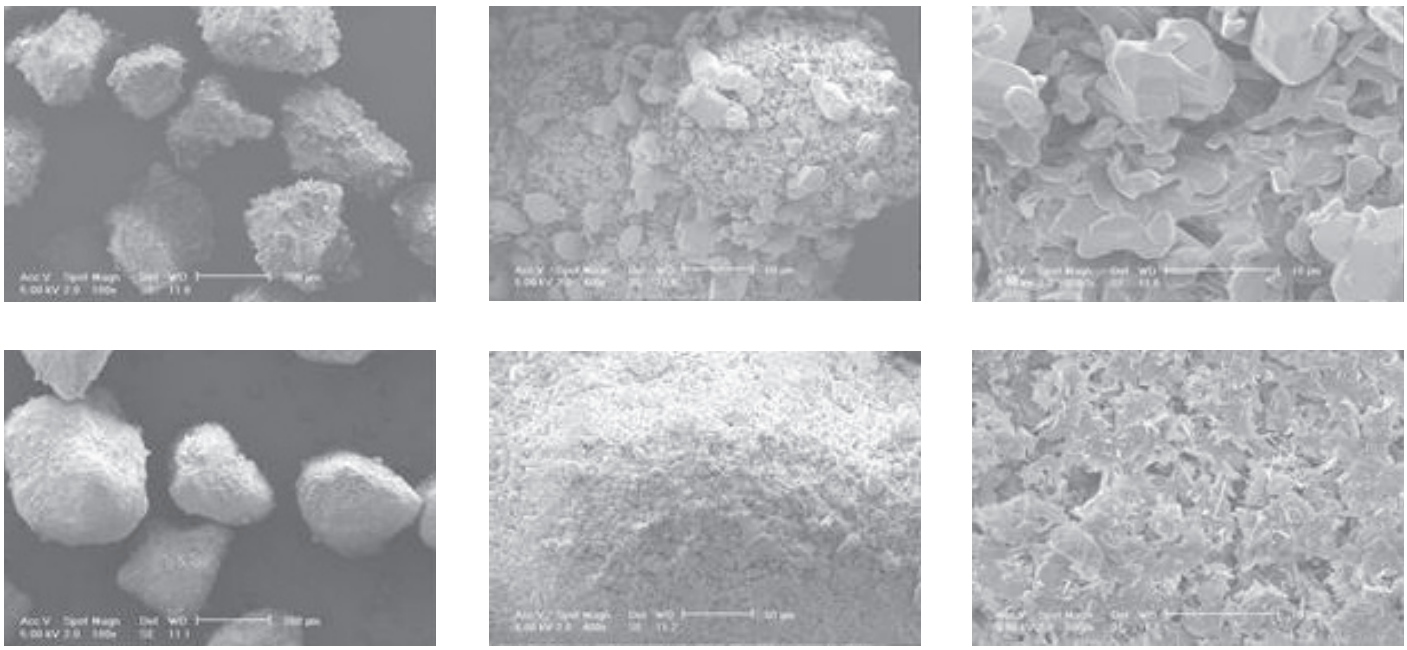

Figure 5: Ibuprofen pellets before (top) and after (bottom) Formulcoat® treatment.

achieved in a continuous way, allowing intrinsically high productivity rates. Labile materials can be processed in this way without any degradation. The main application is taste masking of bitter API for orodispersible formulations.

The cGMP qualification of Pierre-Fabre's new pilot-scale unit is now finished (with a capacity of 10 kg of coated powder per hour) and we are producing GMP batches for bioequivalence studies.

ABOUT THE AUTHOR

Hubert Lochard holds a PhD in Chemical Engineering from Ecole des Mines de Paris, France. He focused his research in the use of supercritical fluid for crystallisation of pharmaceutical compounds.

Then, he joined Pierre Fabre Medicament in order to develop the use of supercritical carbon dioxide in the pharmaceutical field. Dr Lochard is author of dozen publications and patents in this field.